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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12N 15/12, 15/54, C07K 14/47, C12N 9/12, 1/19, 15/81, 1/21, 5/10, 15/85, 15/86, C07K 16/18, 16/40, C12N 15/11, 9/00, A61K 48/00

A1

(11) International Publication Number: **WO 97/37016**

(43) International Publication Date: 9 October 1997 (09.10.97)

(21) International Application Number: PCT/IL97/00117

(22) International Filing Date: 1 April 1997 (01.04.97)

(30) Priority Data:

117800	2 April 1996 (02.04.96)	IL
119133	26 August 1996 (26.08.96)	IL

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: MODULATORS OF TNF RECEPTOR ASSOCIATED FACTOR (TRAF), THEIR PREPARATION AND USE

(57) Abstract

A DNA sequence encoding a protein capable of binding to a tumor necrosis factor receptor-associated factor (TRAF) molecule, TRAF-binding proteins, their isoforms, analogs, fragments and derivatives encoded by the DNA sequence, their methods for the production of the DNA sequences and proteins, and the uses for the DNA sequence and proteins.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/IL 97/00117

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C12N15/54 C07K14/47 C12N9/12 C12N1/19
C12N15/81 C12N1/21 C12N5/10 C12N15/85 C12N15/86
C07K16/18 C07K16/40 C12N15/11 C12N9/00 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K A61K C12Q G01N C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CELL, vol. 83, no. 7, 29 December 1995, pages 1243-1252, XP002032302 ROTHE M ET AL: "THE TNFR2-TRAF SIGNALING COMPLEX CONTAINS TWO NOVEL PROTEINS RELATED TO BACULOVIRAL INHIBITOR OF APOPTOSIS PROTEINS" cited in the application	1-3, 13-17, 21-30, 43-45,49
A	see abstract	6,32-34, 40
	see page 1246, right-hand column, line 29 - page 1248, left-hand column, line 26 see page 1249, right-hand column, line 60 - page 1250, left-hand column, line 38 see page 1250, right-hand column, line 31-44	

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[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
4 August 1997	18. 08. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Macchia, G

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/IL 97/00117

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/17 A61K38/45 C12Q1/68 C12Q1/48 C12Q1/66
G01N33/68 C07K19/00 C12N15/62 //(C12N1/19,
C12R1:865)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 97 06182 A (TULARIK INC) 20 February 1997 see page 3, line 1 - page 13, line 17 see page 30 - page 31; claims --- -/--	1-3, 13-17, 21, 23-25, 27,28, 30, 32-34, 40,44, 45,49

[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
	18. 08. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	NATURE, vol. 385, 6 February 1997, pages 540-544, XP002036441 MALININ N L ET AL: "MAP3K-RELATED KINASE INVOLVED IN NF-kB INDUCTION BY TNF, CD95 AND IL-1" see the whole document	1-4, 6-14, 16-21, 23,24, 30,31, 44-49
P,X	GENES AND DEVELOPMENT, vol. 10, no. 8, 15 April 1996, pages 963-973, XP000607798 CHENG G ET AL: "TANK, A CO-INDUCER WITH TRAF2 OF TNF-AND CD40L-MEDIATED NF-KB ACTIVATION" cited in the application see abstract see page 966, right-hand column, paragraph 2 - page 971, left-hand column	1,6
A	CELL, vol. 80, 10 February 1995, pages 389-399, XP002036476 MOSIALOS G ET AL: "THE EPSTEIN-BARR VIRUS TRANSFORMING PROTEIN LMP1 ENGAGES SIGNALING PROTEINS FOR THE TUMOR NECROSIS FACTOR RECEPTOR FAMILY" cited in the application see abstract see page 394, left-hand column, line 45 - page 395, left-hand column, line 4; figure 6B	1,6
A	TRENDS IN CELL BIOLOGY, vol. 5, October 1995, pages 392-399, XP002036717 VANDENABEELE P ET AL: "TWO TUMOUR NECROSIS FACTOR RECEPTORS: STRUCTURE AND FUNCTION" cited in the application	

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int onal Application No
PCT/IL 97/00117

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9706182 A	20-02-97	AU 6692996 A	05-03-97

INTERNATIONAL SEARCH REPORT

Inter ~tional application No.
PCT/IL 97/00117

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 23-29 as far as in vivo methods are concerned and 40-42 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Form PCT/ISA/210 (continuation sheet)

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

1) claims 1-6, 13-17, 21-30, 32-37, 40, 43-45, 49 all partially.

A DNA sequence encoding a protein capable of binding to tumor necrosis factor receptor-associated factor (TRAF) molecule as depicted in Fig. 3a / Seq.ID:1 / clone 9, fragments, variants and hybridizing molecules thereof. Vectors and transformed host cells. Traf-binding protein encoded by said DNA, isoforms, fragments, analogs and derivative thereof and method for their production. Antibodies. Uses of DNA, protein, antibodies, oligonucleotides, ribozyme for modulation of cell signaling activity mediated by TRAF2. Method for isolating and identifying proteins capable of binding to TRAF2 and of modulating the cellular activity of TRAF2. Pharmaceutical composition comprising said protein, DNA, oligonucleotide, and therapeutical uses thereof. Methods for screening a ligand capable of binding to said protein.

2) claims 7-12, 18-20, 31, 38, 39, 41, 42, 46-48 all totally; claims 1-4, 6, 12-18, 21-30, 32-37, 40, 43, 44, 45, 49 all partially.

A DNA sequence encoding a protein capable of binding to tumor necrosis factor receptor-associated factor (TRAF) molecule as depicted in Fig. 4,6 / Seq.ID:3,6 / clone 10, fragments, variants and hybridizing molecules thereof. Vectors and transformed host cells. Traf-binding protein encoded by said DNA, isoforms, fragments, analogs and derivative thereof and method for their production. Antibodies. Uses of DNA, protein, antibodies, oligonucleotides, ribozyme for modulation of cell signaling activity mediated by TRAF2. Method for isolating and identifying proteins capable of binding to TRAF2 and of modulating the cellular activity of TRAF2. Pharmaceutical composition comprising said protein, DNA, oligonucleotide, and therapeutical uses thereof. Methods for screening a ligand capable of binding to said protein.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

3) claims 1-6, 13-17, 21-30, 32-37, 40, 43-45, 49 all partially.

A DNA sequence encoding a protein capable of binding to tumor necrosis factor receptor-associated factor (TRAF) molecule as depicted in Fig. 5a / Seq.ID:4 / clone 15, fragments, variants and hybridizing molecules thereof. Vectors and transformed host cells. Traf-binding protein encoded by said DNA, isoforms, fragments, analogs and derivative thereof and method for their production. Antibodies. Uses of DNA, protein, antibodies, oligonucleotides, ribozyme for modulation of cell signaling activity mediated by TRAF2. Method for isolating and identifying proteins capable of binding to TRAF2 and of modulating the cellular activity of TRAF2. Pharmaceutical composition comprising said protein, DNA, oligonucleotide, and therapeutical uses thereof. Methods for screening a ligand capable of binding to said protein.